Invited Session: Complex Survival Data

To make the most of the wealth of data from recent longitudinal studies, new models for survival data analysis have been recently developped. They allow to model simultaneously several events and/or recurrent events and/or model jointly the evolution of longitudinal markers accounting for complex observation designs and correlation structures. This session will present some of these recent developments in the field of survival models, multi-state models and joint models.

The invited speakers will be

- Jan Beyersman, Institute of Statistics, Ulm University
- Virginie Rondeau, Biostatistics Team, Bordeaux Population Health Inserm Research Center
- Brian Tom, MRC Biostatistics Unit, University of Cambridge

Non-standard bootstrap for non-standard time-to-event outcomes

Jan Beyersman, Institute of Statistics, Ulm University

Abstract: The motivation behind this talk are outcomes in randomized clinical time-to-event trials where neither Kaplan-Meier-type methodology nor competing risks suffice. In a study on stem cell transplanted leukemia patients, we will aim at demonstrating superiority w.r.t the outcome probability "alive w/o immunosuppressive therapy". In a treatment trial for severe infectious diseases, we will aim at demonstrating non-inferiority w.r.t the outcome probability "cured and alive" on the entire follow-up period. Both of these outcome probabilities are non-monotone, and the first outcome is complicated by immunosuppressive therapy being switched on and off a random number of times. To this end, we will suggest ("wild" or "weird") bootstrapping on the multivariate hazard scale which will be subsequently translated onto probabilities. Comparison of treatment groups will be based on time-simultaneous confidence bands. Unlike the standard bootstrap which draws with replacement from the data, we will not require an i.i.d. data structure, but only general martingale properties. Examples of deviations from an i.i.d. setting are event driven trials in oncology or nested case-control studies. We will also outline how a third bootstrap approach can be used for planning, e.g., of sample size based on published data only.

The use of joint modelling to evaluate failure-times surrogate endpoints

Virginie Rondeau, Biostatistics Team, Bordeaux Population Health Inserm Research Center

Casimir Sofeu-Ledoux and Takeshi Emura

Abstract: A surrogate endpoint can be used instead of the most relevant clinical endpoint to assess the efficiency of a new treatment. Before being used, a surrogate endpoint must be validated based on appropriate methods. Numerous validation approaches have been proposed with the most popular used in a context of meta-analysis, based on a two-step analysis strategy. For two failure-time endpoints, two association measurements are usually used, Kendall's tau at the individual-level and the adjusted

coefficient of determination (R2adj) at the trial-level. However, this adjusted coefficient is not always available due to model estimation constraints. We propose a one-step validation approach based on a joint frailty model, including both individual-level and trial-level random effects. Parameters have been estimated using a semi-parametric penalized marginal log-likelihood method, and various numerical integration approaches were considered. Both individual and trial-level surrogacy was evaluated using a new definition of Kendall's tau and the coefficient of determination. Estimators' performances were evaluated using simulation studies and satisfactory results were found. The model was applied to individual patient data meta-analyses in gastric cancer to assess disease-free survival as a surrogate for overall survival, as part of the evaluation of adjuvant therapy. The proposed joint surrogate model showed satisfactory results compare to the existing two-step copula and one-step Poisson approaches. We proposed a tool to predict the effect of treatment on the true endpoint, based on the observed effect of treatment on the surrogate endpoint. A user-friendly R package associated to this new surrogate endpoints validation approach will be exposed.

Expanded correlated mover-stayer multi-state models for characterising joint activity and damage in the hands of patients with psoriatic arthritis

Brian Tom, MRC Biostatistics Unit, University of Cambridge

In psoriatic arthritis, manifestations of the disease typically result in joints becoming swollen and/or painful (i.e. active joints), which are reversible through treatment or management strategies or spontaneously, and may lead to permanent joint damage. Understanding the interplay between disease activity (as measured by activity in the joints) and damage is of clinical importance as both processes are related to functional impairment. In this talk, we present an expanded multi-state model for the disease activity and damage processes at the individual hand joint level, which accounts for many important features of our cohort of psoriatic arthritis patients from the University of Toronto Psoriatic Arthritis clinic. Firstly, as there are 28 hand joints in a patient and there are extensive lengths of patients' follow-up, we use observation-level multivariate random effects to account for correlation between joints and time-varying unobserved heterogeneity. Secondly, we introduce dynamic covariates which capture the serial correlation due to the disease activity and damage processes' history and relax the Markov assumption. As there is some empirical evidence to suggest that a subset of patients will not progress to damage in the hands, we additionally introduce a mover-stayer component to our model. The models are fitted using maximum likelihood estimation and through both standard and novel parameterisations that provide interpretability, allow us to address important clinical questions regarding pattern of disease, whether damage begets damage, the relationship between disease activity and damage before and after the occurrence of damage and the existence and prevalence of a stayer subpopulation.